

## REMARKS

Claims 1, 2, 18, 20 and 21 are at issue and have been rejected by the Examiner in the present Application. Claims 18 and 20 have been amended and Claims 22-25 have been added. Therefore, Claims 1, 2, 18, and 20-24 are at issue. The Examiner's rejections are as follows:

- (1) Claim 1 is rejected under 35 U.S.C. §103(a) as being allegedly obvious.
- (2) Claims 1, 2, 18, 20 and 21 are rejected under 35 U.S.C. §103(a) as being allegedly obvious.

Applicants believe the present amendments and following remarks traverse the Examiner's rejections of the Claims. These remarks are presented in the same order as they appear above.

### **I. No *Prima Facie* Case of Obviousness is Established For Claim 1.**

The Examiner has rejected Claim 1 under 35 U.S.C. §103(a) as being unpatentable over Namikawa *et al.* (*J. of Immun.* 128: 932-934, February 1982) in view of Tobin *et al.* (US Pat. 5,674,978) and prior art disclosed in the Specification (Alvord *et al.*, Zamvil *et al.*, and Kimball). Applicants respectfully traverse this rejection.

The combination of references referred to by the Examiner fails to provide a *prima facie* showing of obviousness as required by §2143 of the Manual of Patent Examining Procedure (MPEP). There are three criteria which must be met to provide *prima facie* obviousness. The first of these is a suggestion or motivation in the references or the knowledge generally available to combine the reference teachings. The second is the prior art must teach or suggest all the claim limitations. The third is a reasonable expectation of success should the combination be carried out. Applicants submit that the Examiner has failed to set forth a *prima facie* case of obviousness because the combination does not teach all the claim limitations, there is no motivation to combine, and there is no reasonable expectation of success if the art is combined.

**A. No Motivation Exists to Form This Combination**

No motivation exists to combine these references as suggested by the Examiner. To establish a *prima facie* case of obviousness, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference teachings." MPEP §2143.

The Examiner points to the references themselves in an attempt to establish a motivation for combining the references. Specifically, the Examiner combines the cited art stating, "Namikawa et al. teach that immunization with MBP in IFA prevents EAE in rats..." and "[o]ne of ordinary skill in the art would have been motivated to ... [form the claimed invention] ... because Tobin *et al.* teach treatment with autoimmune antigens for the treatment of human disease." (Office Action, pg 2).

While the Examiner continues to assert the Namikawa reference, it cannot be disputed that the Namikawa reference lacks any specific teaching regarding treatment of 1) humans with autoimmune symptoms (such as is claimed in Claim 25) and 2) humans to protect them against autoimmune disease. When one reads the discussion section of the Namikawa paper, one sees no suggestion to extend the work to humans - indeed, no suggestion that the work described in the paper has any particular application to prevention or treatment of autoimmune disease!

Similarly, while the Examiner continues to assert the Tobin reference, the Tobin reference is concerned with GAD and does not teach immunization with MBP. Tobin *et al.* discusses treating Insulin-dependent diabetes mellitus (IDDM) with glutamic acid decarboxylase (GAD) peptides, not treating multiple sclerosis with MBP in IFA.

How then does the Examiner justify the combination? Why would one skilled in the art combine the teachings of these disparate references?

In the instant Office Action, the Examiner states "the motivation to combine is reasoned from the knowledge generally available to one of ordinary skill in the art and established scientific principles." (Office Action, pgs 3-4). And yet, the Examiner does not describe what this general knowledge is or where it comes from, and does not point to anything in the record to provide the motivation. As such, since no motivation exists to combine the prior art references cited by the Examiner, no *prima facie* case has been established and the claims should be allowed.

**B. No Reasonable Expectation of Successfully Combining the Art Exists**

In order to establish a *prima facie* case of obviousness the prior art must, when combined, lead to a reasonable expectation of successfully producing the invention. MPEP § 2143.02. Applicants submit that one of ordinary skill in the art would not reasonably expect to produce the claimed invention by combining the cited references.

The Examiner combines Namikawa *et al.* and Tobin *et al.* to purportedly arrive at the claimed invention. (Office Action, pg 2). However, where is the teaching in the art that the experiments with GAD in the Tobin reference can be extended to any other autoimmune disease? Why would one of ordinary skill in the art have had a reasonable expectation of *success* using MBP/IFA to protect humans from multiple sclerosis - when the Tobin reference is silent concerning MS?

It appears that the Examiner, using hindsight gained from a reading of the present specification, has genericized the Tobin reference teachings beyond the boundaries of the four corners of the Tobin patent. There is clearly no basis for doing so. Indeed, the confusing results of the Namikawa reference teach against such a generic approach. More specifically, Namikawa reports that MBP/IFA treated animals can transfer EAE!

In the present Office Action, the Examiner addresses this problem with Namikawa by arguing that the claims do not involve the transfer of cells from an immunized donor. This argument by the Examiner misses the point. The rejection is not a 102 rejection - it is a 103 rejection. The rejection is based on a combination of art - a combination which cannot be made without justification! Under law, the Examiner must examine the reference *as a whole* to determine what it teaches to one skilled in the art. It is submitted that the transfer experiments teach one skilled in the art that the *results* of treatment with MBP/IFA are **not** clear. Indeed, anyone who reads the discussion section of the Namikawa paper will understand that the authors are unable to explain the seemingly discrepant results - *thus raising the question as to whether the results can be relied upon!*

Since the results are not clear in the Namikawa reference, the Examiner can use it as justification to broaden the teachings of the Tobin reference. Since there is no other reference of record, no *prima facie* case of obviousness is established and the claims should be allowed.

**II. No *Prima Facie* Case of Obviousness is Established For Claims 1, 2, 18, 20 and 21, or New Claims 22-25.**

The Examiner has rejected Claims 1, 2, 18, 20 and 21 under 35 U.S.C. §103(a) as being unpatentable over Namikawa *et al.* in view of Tobin *et al.*, the prior art disclosed in the Specification (Alvord *et al.*, Zamvil *et al.*, and Kimball), and further in view of Goodwin *et al.* (U.S. Pat. 5,569,585) and Oprandy (U.S. Pat. 5,200,312). Applicants respectfully traverse this rejection because the Examiner has failed to establish the requirements of a *prima facie* case of obviousness.

**A. No Motivation Exists to Combine the Art as Suggested by the Examiner**

No motivation exists to combine the cited references as suggested by the Examiner. To establish a *prima facie* case of obviousness, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference teachings." MPEP §2143.

The Examiner combines Namikawa *et al.* and Goodwin *et al.* in an attempt to yield the present invention. In an effort to establish a motivation to combine these references, the Examiner points to the cell proliferation assay in Namikawa *et al.*, modifying it to produce a cytokine binding assay by combining Goodwin *et al.* The Examiner justifies this stating "[t]he response of T cells would have been alternatively measured using art known lymphokine assays, because the art recognizes that activated T cells produce lymphokines in response to antigenic stimulation... ". (Office Action, pg 4). The mere fact that the prior art may be modified in the manner suggested by the Examiner, however, does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Fritch*, 23 USPQ 2d 1780, 1783–84 (Fed. Cir. 1992). In this case, Namikawa *et al.* does not suggest why the cytokine production of T cells would be desirable. Namikawa *et al.* does not even mention measuring cytokines. The fact that Goodwin *et al.* describes a cytokine binding assay for activated T cells can be performed, does not provide the motivation why one skilled in the art would run this assay on the MBP/IFA activated cells of Namikawa *et al.* As such no motivation to combine is established for Claims 2, 18, and 20-26.

Claim 18 has additional limitations that even further destroy the motivation to combine. Part e) of Claim 18 requires the cytokines to be detected in order to detect Th1 and

Th2 directed immunity. None of the cited references indicate that detecting cytokines is a way to determine what type of T helper cells are activated. As such, no motivation exists to combine/modify the art in such a way to produce Claim 18 (or dependent Claims 20-24). As there is no motivation to combine the references as suggested by the Examiner, no *prima facie* case of obviousness is established, and all the Claims should be allowed.

**B. The Combination Does Not Teach All the Claim Limitations**

To establish a *prima facie* case of obviousness the prior art must teach or suggest all the claim limitations. MPEP §2143.03. Applicants submit that even if the prior art is combined, the resulting combination fails to teach every element of Claims 1, 2, 18, 20, 21, and new Claims 22-26.

The arguments regarding Claims 1 and 25 set forth above are incorporated here. In regard to Claim 18, the combined prior art fails to teach every Claim limitation. The Examiner cites an assay in Namikawa *et al.* in which the proliferation of T cells in response to MBP is measured. (Office Action, pg 4). Clearly, this reference does not teach the cytokine detecting assay in the instant Claims as cytokines are not being measured. The Examiner also cites Goodwin *et al.* as teaching a cytokine detection assay, arguing that it could be used to detect the MBP/IFA cells of Namikawa *et al.* (Office Action, pg 4). Specifically the Examiner states "[t]he response of T cells [of Namikawa *et al.*] would have been alternatively measured using art known lymphokine assays, because the art [Goodwin *et al.*] recognizes that activated T cell produce lymphokines in response to antigenic stimulation... ". (Office Action, pg 4). Applicants submit that even if the art is combined, it fails to teach every element of Claim 18 (and thus dependent Claims 20-24).

Without waiving this argument, but in order to further Applicants' business interests and the prosecution of the present Application, yet without acquiescing to the Examiner's arguments, and without waiving the right to prosecute the original Claims in the future, Applicants have amended Claim 18. Step e) in Claim 18 now requires that the cytokines secreted by the T cells be detected in order "to detect Th1 and Th2 directed immunity generated in said human." This amendment finds full support in the Specification (See Specification, pg 8, and Example 3). The combined prior art does not teach this claim limitation. In particular, Goodwin *et al.* only teaches detecting a particular cytokine, without

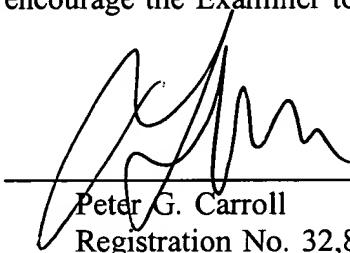
anything further. (Goodwin *et al.*, col. 10, lines 53-55). Goodwin *et al.* does not teach detecting particular cytokines in order to determine which type of T helper (Th) cells are producing the cytokine. As such, this Claim limitation is not taught and no *prima facie* case of obviousness is established for Claim 18 (and dependent Claims 20-24).

In regard to Claims 23 and 24, the combined prior art fails to teach the use of multiple cytokine binding ligands required in these Claims. Goodwin *et al.* describes the use of "a monoclonal antibody to the cytokine to be measured..." (Goodwin *et al.*, col. 10, lines 53-54). Claims 23-24 both require the use of two types of monoclonal antibodies to detect cytokines. Claim 24 further requires particular monoclonal antibodies in specific pairs with six different possible combinations. The combined prior art does not specify multiple monoclonal antibodies, let alone specific combinations. As such, every element in these Claims is not taught by the prior art. Consequently, no *prima facie* case of obviousness is established and Claims 23 and 24 should be allowed.

### Conclusion

Applicants submit that, with due consideration of all the factors discussed above, the patentability of the Claims is evident. For the foregoing reasons, it is submitted that the Examiner's rejections of the Claims was erroneous, and reversal of these rejections is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this Application, Applicants encourage the Examiner to call the undersigned collect at (617)-252-3353.

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